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Synthesis, Characterization and Evaluation of Biological Activity of Novel Heterocyclic Derivatives from Azomethine Compounds

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ABSTRACT

This research describes the synthesis of new seven-membered heterocyclic derivatives as 1,3-oxazepine-dione derived from azomethine compounds. Azomethine compounds R_1-R_4 were synthesized by the reaction of aromatic aldehydes with primary aromatic amines. The novel compound of 1,3-oxazepine-dione derivatives R_5-R_9 were obtained from the treatment of azomethine compounds with anhydrides. The synthesized compounds were checked by TLC technique, spectral methods (FT-IR, H^1-NMR) and measurements of some its physical properties. The biological activity of the heterocyclic derivatives was investigated against bacteria and fungi *in vitro*.

Keywords: Azomethine, Anti-fungal, Anti-bacterial, 1,3-oxazepine.

INTRODUCTION

Azomethine are the compounds containing (-HC=N-) group, the best and easiest method of azomethine synthesis is the condensation reaction between the carbonyl group (C=O) of ketones or aldehydes and the amino group (NH_2) of primary amines[1-4]. The equivalent rate 2:1 of 3-bromo benzaldehyde and 1,3- diamino propan- 2-ol gave the azomethine compound described in the following reaction[5].

Oxazepines are heterocyclic compounds of the seven-membered ring with two heteroatoms (O and N), the oxygen atom is located at position 1 and a nitrogen atom in positions -2, -3 or -4[1]. To a solution of 0.01 mole of azomethine in dry toluene, a solution of maleic anhydride 0.02 mole in ethanolic solution was added dropwise with stirring then refluxed for 3-4 hours[6]. The reaction of the following azomethine compound with phthalic anhydride in dry benzene gave substituted oxazepine derivatives[7].

In this study, the synthesized compounds have been proven by TLC techneque and melting point assay. Their structures have been characterized by ^{1}H-NMR and FT-IR spectroscopic methods. The antifungal and antibacterial activity of the synthesized 1,3-oxazepine-dione derivatives were studied against *Geotrichum* sp., *Escherichia* coli, *Klebsiella* sp. and *Staphylococcus aureus*.

EXPERIMENTAL

MATERIALS AND METHODS

Aldehydes, mines and other chemicals were purchased from Sigma Aldrich. Melting points were recorded on Electrothermal Melting point Apparatus (uncorrected). FT-IR spectra were recorded at room temperature from 4000-400 cm^{-1} with KBr disc on Infrared Spectrophotometer Model Tensor 27 Bruker Co., Germany. The ^{1}H-NMR spectra were recorded on Bruker Ac-300MHz spectrometer.

General Procedure for the synthesis of azomethine compounds R_1-R_4

Equimolar mixtures 0.01 mole of aromatic amines and 0.02 mole of aromatic aldehydes dissolved in 25 mL absolute ethanol was placed in a 100 mL round-bottom flask. 3-4 drops of glacial acetic acid was added as catalyst, the mixture was allowed to react at reflux temperature for 4 h and then let to cool down to the room temperature, the progress of the reaction and the purity of the compounds were monitored with TLC technique, whereby a crystalline solid was separated out and recrystallized from ethanol, the structural formula, names, melting points, colors and percentage of yields for the synthesized azomethine compounds R_1-R_4 are recorded[8-12].

General Procedure for the synthesis of 1,3-oxazepine-dione derivatives R_5-R_9

Equimolar mixtures 0.01 mole of azomethine compounds and 0.02 mole anhydride compounds dissolved in 30 mL of tetra hydro furan (THF) placed in a 100 mL round-bottom flask, the reaction mixture was refluxed for 3 h the progress of the reaction and the purity of the compounds were monitored with TLC technique then solid product was precipitated, filtered off and recrystallized from ethanol, the structural formula, names, melting points, colors and percentage of yields for the synthesized 1,3-oxazepine-dione derivatives R_5-R_9 were recorded[13,14].

Anti-fungal and anti-bacterial activity of synthesized 1,3-oxazepine-dione derivatives R_5-R_9

Anti-microbial activity of the derivatives against *Geotrichum* sp., *E. coli*, *Staphylococcus aureus* and *Klebsiella* sp. Using well diffusion method on Mueller Hinton Agar plates. The well diameter is 6 mm. The zone of inhibition was recorded as antimicrobial activity. About 6 µg $well^{-1}$ of chemicals in DMSO introduced into the bore wells on the agar using a sterile dropping pipette. The extracts were allowed to diffuse before inoculated with the yeast then incubated at 37°C for 24 hour. The plates were examined for measuring any inhibition zone[15]. About 50 µg Gentamycine per well was used as a positive control and 50 µl DMSO was used as a negative control.

RESULTS AND DISCUSSION

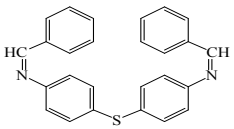
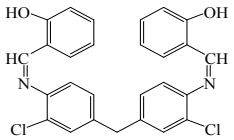
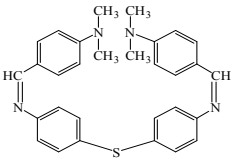
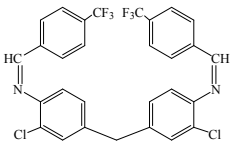
Chemistry

Tables 1 and 2 exhibited structural formula, nomenclature, the percentage of yield, melting point and the color of all prepared compounds. The best yield of the synthesized azomethine was for compounds R_1 86% and R_3 85%, while the lower yield was for compound R_2 78% and the best yield of the synthesized 1,3-oxazepine-dione derivatives was for R_5 89% while the lower yield was for R_7 73%. The higher melting point for azomethine compounds was for compound R_3, the lower melting point was for compound R_4, while the higher melting point of the synthesized 1,3-oxazepine-dione derivatives was for compound R_9, the lower melting point was for compound R_5. The different colors, melting points and the number with distance of spots in the TLC technique to the products compared with the raw material are initial evidence of interaction.

Characterization of synthesized azomethine compounds R_1-R_4

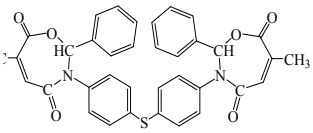
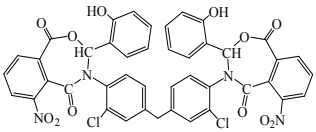
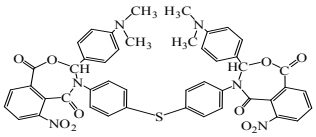
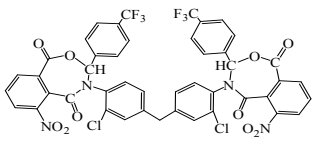
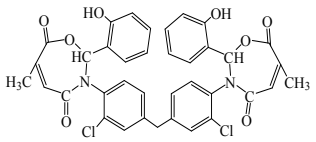
Azomethine compounds were synthesized from commercially available aldehydes and primary amines. TLC technique was used to follow the chemical reaction, the synthesized azomethine identified by their melting points and FT-IR spectra. The FT-IR spectra showed the appearance of the stretching absorption bands of azomethine (HC=N-) at 1601-1628 cm^{-1} indicative of the formation of the resulting azomethine compounds, (C-N) at 1154-1167 cm^{-1}, (C-S) at 687-692 cm^{-1}, (C-Cl) at 933-937 cm^{-1} beside the characteristic bands of the residual groups in the structure[16].

Table 1: Structural formulas, nomenclature, melting points, colors and % yields of azomethine compounds R_1-R_4

Compound	Structural formula	Nomenclature	Yield%	m. p. °C	Color
R_1		N,N'-(thiobis(4,1-phenylene))bis (1-phenyl methanimine)	86	168-170	Silver
R_2		2,2'-((1Z,1'Z)-((methylenebis(2-chloro-4,1-phenylene))bis (azanyly lidene))bis(methanylylidene)) diphenol	78	200-202	Yellow
R_3		4,4'-(((thiobis(4,1-pheny lene)) bis (azanylylidene))bis (methanylylid ene))bis(N,N-di methyl aniline)	85	220-222	Dark Yellow
R_4		(1Z,1'Z)-N,N'-(methylene))bis(2-chloro-4,1-phenylene))bis (1-(4-(tri fluoromethyl)phenyl)methanimine)	80	95-96	Light Yellow

[a]Melting point (Celsius)

Table 2: Structural formulas, nomenclature, melting points, colors and % yields of the synthesized 1,3-oxazepine-dione derivatives R_5-R_9

Compound	Structural formula	Nomenclature	Yield%	m. p. °C	Color
R_5		3,3'-(thiobis(4,1-phenylene))bis (6-methyl-2-phenyl-2, 3-dihydro-1,3-oxazepine-dione)	89	80-82	Orange
R_6		4,4'-(methylenebis(2-chloro-4,1-phenylene)) bis(3-(2-hydroxy phenyl)-9-nitro-3,4-dihydrobe nzo [e] 1,3-oxazepine-dione)	84	198-200	Yellow
R_7		4,4'-(thiobis(4,1-phenylene))bis (3-(4-(dimethylamino)phenyl)-9-nitro-3,4-di hydro benzo [e] 1,3-oxazepine-dione)	73	135-137	Red
R_8		4,4'-(methylenebis(2-chloro-4,1-phenylene)) bis(6-nitro-3-(4-(triflu oromethyl) phenyl) -3,4-di hydro benzo[e] 1,3-oxazepine-dione)	87	188-190	Yellow
R_9		3,3'-(methylenebis(2-chloro-4,1-phenylene)) bis(2-(2-hydroxy ph enyl)-6-methyl-2,3-di hydro-1,3-oxazepine-dione)	79	203-204	Light Yellow

[a]Melting point (Celsius)

The previous studies suggest that the aromatic aldehyde which contain such a -N$(CH_3)_2$ group at para position decreases the reaction speed when condensing with aromatic amine, while the reaction speed increases when such a -CF_3 group in the same site on the aromatic aldehyde ring because the drawing electrons group such a -CF_3 increase the the positive charge of the carbon of the carbonyle group (C=O) in aromatic aldehyde, while the donor electrons group such a -N$(CH_3)_2$ decrease the the positive charge of the carbon of the carbonyle group (C=O) in aromatic aldehyde, glacial acid is used as a catalyst to increase the electrophile of the carbonyl group (C=O) to accelerate the reaction and increase the precentage yield. See Table 3 and FT-IR spectra of R_3 and R_4 compounds (Figure 1).

Table 3: FT-IR of azomethine compounds R_1-R_4

Compound	FT-IR[a], ν(cm^{-1})[b]						
	C=N	C-N	C=C Aromatic	C-H Aromatic	C-H Aliphatic symmetric	C-H Aliphatic Asymmetric	Others
R_1	1617	1166	1572	3028	--	--	C-S: 692
R_2	1616	1154	1598	3052	2937	2987	O-H: 3500
R_3	1601	1163	1574	3055	2886	2977	C-S: 687
R_4	1628	1167	1578	3067	2908	2989	C-F: 1307

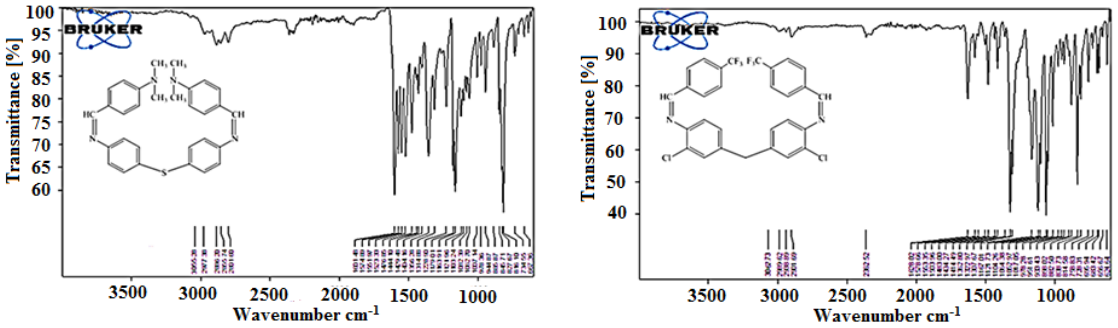


Fig. 1. FT-IR spectra of R_3 and of R_4

The mechanism of azomethine compounds formation involves a nucleophile attack of the electron pair of NH_2 amine on the C=O of aldehyde to form a hemiaminal N-substituted medium that loses a water molecule to give the stable compound (azomethine). The reaction is believed to occur in the following mechanism[17]. See (Figure 2).

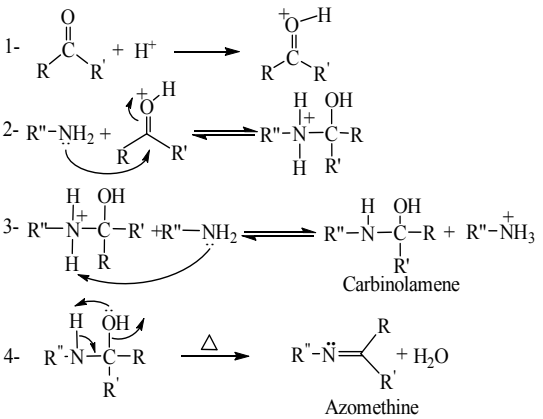


Fig. 2. Mechanism of azomethine compounds formation

Characterization of synthesized 1,3-oxazepine-dione derivatives R_5-R_9

Synthesis of 1,3-oxazepine- dione derivatives was achieved by the reaction of azomethine group (HC=N-) with anhydride. TLC techneque used to follow the chemical reaction, the resulted products were identified by their melting points, FT-IR and ^{1}H-NMR spectra. The FT-IR spectra of the products showed disappearance of the absorption bands of the (C=N) of the azomethine compounds and the stretching absorption bands of two anhydride compounds and showed the appearance of the stretching absorption at 1608-1650 cm^{-1} indicative of C=O lactam bonds, stretching absorption at 1698-1728 cm^{-1} indicative of C=O lacton bonds, stretching absorption at 1277-1285 cm^{-1} indicative of C-O bonds, stretching absorption at 1185-1203 cm^{-1} indicative of C-N bonds, stretching absorption at 676-683 cm^{-1} indicative of C-S bonds, stretching absorption at (1345-1363)-(1482-1533) cm^{-1} indicative of NO_2 group, beside the characteristic bands of the residual groups in the structure[18]. See Table 4 and FT-IR spectra of R_7 and R_8 compounds (Figure 3).

Table 4: FT-IR of the 1,3-oxazepine-dione derivatives R_5-R_9

Compound	FT-IR[a] (KBr), ν(cm^{-1})[b]								
	C=C Aromatic	C-O	C-H Aromatic	C-N	C=O Lactam	C=O Lacton	C-H Aliphatic Asymmetric	C-H Aliphatic Symmetric	Others
R_5	1586	1277	3102	1203	1624	1698	2886	2975	C-S: 682
R_6	1559	1280	3049	1187	1608	1701	2920	2985	O-H:3470
R_7	1599	1285	3098	1185	1650	1728	2897	2934	C-S: 676
R_8	1573	1278	3042	1196	1629	1698	2891	2939	C-F: 1307
R_9	1562	1282	3054	1186	1614	1715	2929	2988	O-H:3480

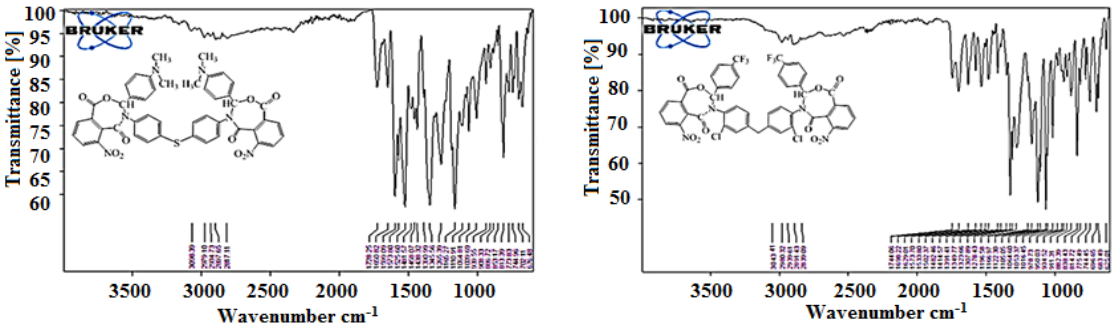


Fig. 3. FT-IR spectra of R_7 and R_8

The ^{1}H-NMR spectrum of R_5 in solvent DMSO showed chemical shifts (δ ppm) as folllows: the singlet at 1.98 indicates the presence 6H of the two groups of (CH_3), the singlet at 6.08 indicates the presence 2H of the two groups of (=CH), the singlet at 10.25 indicates the presence 2H of the two groups of (N=CH), multiplet at 7.24-7.95 indicates the presence 18H of the aromatic protons and the spectrum of R_6 showed chemical shifts (δ ppm) as follows: the singlet at 4.04 indicates the presence 2H of the group (CH_2), the singlet at 9.02 indicates the presence 2H of the two groups of (N=CH), the singlet at 13.16 indicates the presence 2H of two groups of (-OH), multiplet at 6.97-7.68 indicates the presence 20H of the aromatic protons[19]. Other chemical shifts (δ ppm) of compounds R_7-R_9 are given in (Table 5). See ^{1}H-NMR spectra of R_6 and R_9 compounds (Figure 4).

Table 5: The ^{1}H-NMR Spectra of the 1,3-oxazepine-dione derivatives R_5-R_9 in DMSO

Compound	Chemical Shift δ ppma
R_5	Singlet in 1.98 for (6H, 2 CH_3), singlet in 6.08 for (2H, 2 =CH), singlet in 10.25 for (2H, 2 N-CH), multiplet in 7.24-7.95 for (18H, aromatic protons).
R_6	Singlet in 4.04 for (2H, CH_2), singlet in 9.02 (2H, 2 N-CH), singlet in 13.16 (2H, 2 -OH), multiplet in 6.97-7.68 (20H,aromatic protons).
R_7	Singlet in 3.03 for (12H, 4 N-CH_3), singlet in 9.67 for (2H, 2 N-CH), multiplet and doublet of doublet in 6.78-8.44 for (22H, aromatic protons).
R_8	Singlet in 4.01 for (2H, CH_2), singlet in 10.13 for (2H, 2 N-CH), multiplet and doublet of doublet in 6.69-8.71 for (20H, aromatic protons).
R_9	Singlet in 3.09 for (6H, 2 CH_3), singlet in 4.04 for (2H, CH_2), singlet in 5.20 for (2H, 2 =CH), singlet in 9.02 for (2H, 2 N-CH), singlet in 13.16 for (2H, 2 -OH), multiplet in 6.97-7.68 for (14H, aromatic protons).

[a]The references point (the chemical shift of tetramethylsilane $(CH_3)_4Si$).

The both reactions of the synthesized azomethine compounds with two anhydrides are given by the following equations (Figure 5).

It may be concluded that both reactions take place via interaction between HOMO orbital of anhydrides with LUMO orbital of (C=N) group by concerted dipolar cycloaddition mechanism as represented in the following reaction[20], see Figure 6.

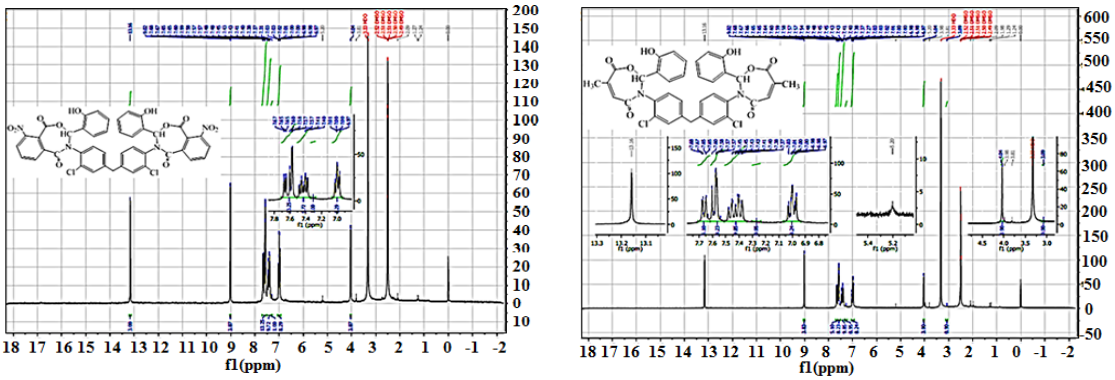


Fig. 4. ^{1}H-NMR Spectra of R_6 and R_9

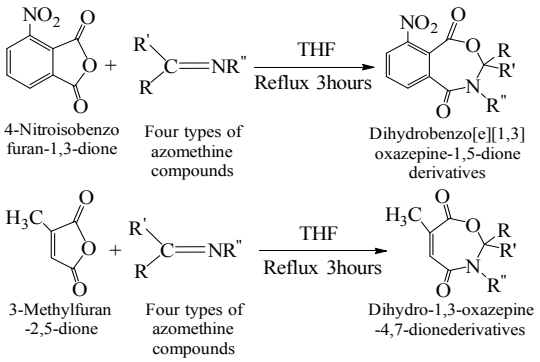


Fig. 5. Structure of the synthesized 1,3-oxazepine-dione derivatives from two types of anhydrides

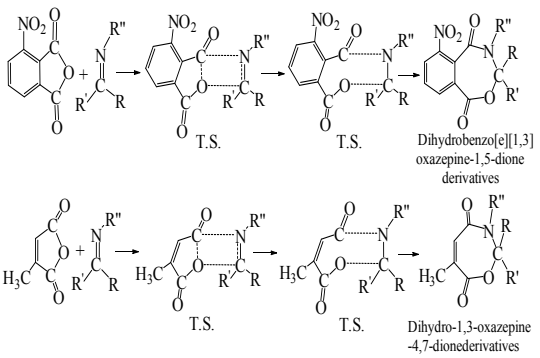


Fig. 6. Mechanism of 1,3-oxazepine-dione derivatives formation for two types of anhydrides

The mechanism involves the addition of one σ-carbonyl to π-bond (C=N) to give 4-membered cyclic and 5-membered cyclic ring of anhydride in the same transition state [T.S.], which opens into 4-nitroisobenzofuran-1,3-dione and 3-methylfuran-2,5-dione anhydrides to give seventh-membered cyclic ring 1,3-oxazepine-dione derivatives[21].

The antifungal and antibacterial activity of 1,3-oxazepine-dione derivatives R_5-R_9

Table 6 exhibited that the higher zone of inhibition was 18.3 mm by compound R_8 against *S. aureus*, followed 14.6 and 14.0 mm by the same compound against *Klebsiella* sp. and *E. coli*, respectively. The lower zone of inhibition was 8.0 mm by compound R_9 against *S. aureus* and *E. coli*, and by compound R_6 toward *E. coli*. While, compound R_6 did not inhibit other microbes in this test. Also, the compounds R_5 and R_9 did not inhibit *Geotrichum* sp. and *Klebsiella* sp., respectively. The role of these compounds may be linked and destroyed the cell wall of microbes or stopped replication of microbial DNA[22,23]. The differences in the inhibitory effect related to the chemical synthesis of each compound as above, see Fig. 7 and 8. Gentamycin showed the inhibition zone approx. 26 mg while the negative control (50 µl DMSO) did not exhibit any inhibition zone.

Table 6: Zone inhibition of the synthesized 1,3-oxazepine-dione derivatives R_5-R_9

Pathogenic fungi and bacteria	Zone inhibition (mm)[a]					Gentamycin[b]	DMSO[c]
	R_5	R_6	R_7	R_8	R_9	50 µg/well	50 µg/well
Geotrichum sp.	0	0	11.1	12	0	26	0
E. coli	9	8	11.6	14	8	27	0
S. aureus	9	0	11A.1	18.3	8	26	0
Klebsiella sp.	9	0	10	14.6	0	25	0

[a]Zone inhibition of the milimeter unit. [b]The positive control. [c]The negative control.

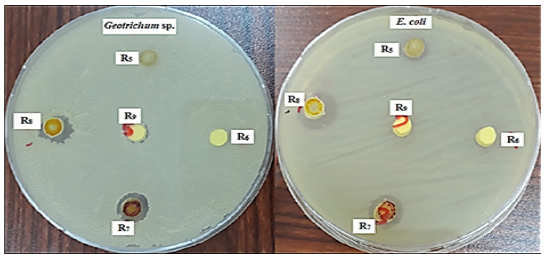


Fig. 7. Antimicrobial activity of the synthesized 1,3-oxazepine-dione derivatives R_5-R_9 in DMSO against *Geotrichum* sp. and *E. Coli*

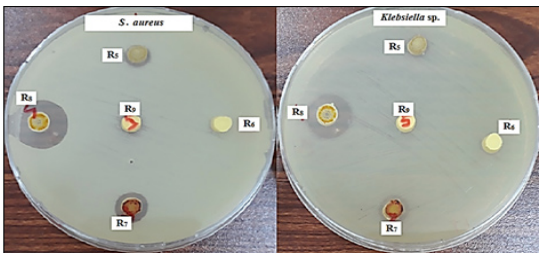


Fig. 8. Antimicrobial activity of the 1,3-oxazepine-dione derivatives R_5-R_9 in DMSO against *S. aureus* and *Klebsiella* sp

CONCLUSION

The formation of stable seventh- membered heterocyclic derivatives as (dihydro-1,3-oxazepine-4,7-dione) and (dihydrobenzo [e] [1,3]oxazepine-1,5-dione) has been achieved by the interaction between HOMO orbital of anhydrides with LUMO orbital of (C=N). The results of FT-IR and ^{1}H-NMR showed that the target molecules were formed due to the least obstructive effect in all preparation processes. TLC technique identified the synthesized compounds; this makes for all the synthesized compounds with high purity. Generally, R_8 derivative is the best derivative that has significantly ($p<0.01$) recorded a stronger influence to inhibit the growth of all types of bacteria and fungi, while R_6 derivative has recorded inhibition against one of the types of bacteria and fungi. Slight variation in the structure of those derivatives can show the very dramatic effect on the efficiency of these compounds in their bio-activity. The present work may be helpful in designing more potent antifungal and antibacterial agents for therapeutic use in the future.

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Conflicts of Interest

The authors declare no conflict of interest.

REFERENCES

1. El-ajaily, M.; Maihub, A.; Mahanta, U.; Badhei, G.; Mohapatra, R. P.; Das, mixed ligand complexes containing Schiff bases and their biological activities: a short review, *Rasayan J. Chem.*, **2018**, *11*, 166-174.
2. Nastasa, C.; Vodnar, D.; Ionu ¸ I.; Stana, A.; Benedec, D.; Tamaian, R.; Oniga, O.; Tiperciuc, B.; Antibacterial Evaluation and Virtual Screening of New Thiazolyl-Triazole Schiff Bases as Potential DNA-Gyrase Inhibitors, *Int. J. Mol. Sci.*, **2018**, *19*, 1-18.
3. Bavane, J.; Mohod, R.; Synthesis, characterization and electrochemical studies of symmetrical schiff base complexes of [1-(5 chloro-2-hydroxy-4-methyl- phenyl) ethanone-4-chloro (-3-trifluro methyl) aniline], *Pharma Innov. J.*, **2018**, *7*, 149-152.
4. Vadivel, R.; Jayakumar, R.; Ananthi, N.; Promising Antibacterial Activity of Simple Schiff Bases, *Org. Med. Chem. Int. J.*, **2018**, *5*, 1-6.
5. Warad, I.; Abedalrazeq, H.; Amer, N.; Al-Nuri, M.; Al-Ali, A.; Al-Zaqri, N.; Shivalingegowda, N.; 1,3-Bis[(E)-(3-bromobenzylidene) amino] propan-2-ol, *Molbank.*, **2017**, *7*,1-7.
6. Mohammed-Ali, M.; Salman, H.; Abdul-Hussein, Z.; Synthesis, Characterization and Antibacterial Activity of Some New Oxazepine compounds, *J. Thi-Qar Sci.*, **2014**, *5*, 32-37.
7. Younus, A.; Jaber, N.; Synthesis and Characterization a New 1,3-Oxazepine Compounds from New Bis-4-Amino-3-mercapto-1,2,4-triazole Derivatives, *Org. Chem.: Indian J.*, **2016**, *12*, 1-12.
8. Iftikhar, B.; Javed, K.; Khan, M.; Akhter, Z.; Mirza, B.; Mckee, V.; Synthesis, characterization and biological assay of Salicylaldehyde Schiff base Cu (II) complexes and their precursors, *J. Mol. Struct.*, **2018**, *1155*, 337-348.
9. Jawoor, S.; Patil, S.; Toragalmath, S.; Synthesis and characterization of heteroleptic Schiff base transition metal complexes: a study of anticancer, antimicrobial, DNA cleavage and anti-TB activity, *J. Coord. Chem.*, **1018**, *71*, 271-283.
10. Kadhim, K.; Munahi, M.; Synthesis, Characterization and Biological Evaluation of Some Novel Schiff'S Bases Derived from Vanillin, *J. Glob. Pharm. Technol.*, **2017**, *10*, 383-386.

11. Azam, M.; Al-Resayes, S.; Wabaidur, S.; Altaf, M.; Chaurasia, B.; Alam, M.; Shukla, S.; Gaur, P.; Talmas, N. ; Albaqami, M.; Islam, M.; Park, S.; Synthesis, Structural Characterization and Antimicrobial Activity of Cu (II) and Fe (III) Complexes Incorporating Azo-Azomethine Ligand, *Molecules*., **2018**, *23*, 1-13.
12. Al Zoubi, W.; Al–Hamdani, A.; Ahmed, S.; Ko, Y.; a new azo-Schiff base: Synthesis, characterization, biological activity and theoretical studies of its complexes, *Appl Organometallic Chem*., **2018**, *32*, 1-15.
13. Al-Sultani, K.; Synthesis, identification and evaluation tha biological activity for some new heterocyclic compounds derived from Schiff bases, *IOSR J. Appl. Chem*., **2017**, *12*, 39-47.
14. H. Sadiq, *World J. Pharm. Pharm. Sci*., **2017,** *6*, 186-198.
15. Owaid, M.; Raman, J. ; Lakshmanan, H.; Al-Saeedi, S.; Sabaratnam, V.; Al-Assaffii, I.; Mycosynthesis of silver nanoparticles from Pleurotus cornucopiae var. citrinopileatus and its inhibitory effects against *Candida* sp., *Mater. Lett*., **2015**, *153*, 186-190.
16. Silverstein, R.; Webster, F.; Kiemle D.; Spectrometric identification of organic compounds, John Wiley and sons, Inc., 7th edition., **2005**, 72-126.
17. Al-Juburi, R.; Synthesis and Characterization of Some Heterocyclic Compounds (Oxazepine, Tetrazole) Derived from Schiff Bases, Journal of Al-Nahrain University., **2012**, *15*, 60-67.
18. Altintop, M.; Çiftçi, G.; Temel, H.; Synthesis and evaluation of new benzoxazole derivatives as potential antiglioma agents, *Marmara Pharm. J*., **2018**, *22*, 547-558.
19. Silverstein, R.; Webster, F.; Kiemle, D.; Spectrometric identification of organic compounds, John Wiley and sons, Inc., 7th edition., **2005**, 127-202.
20. Al- Bayati, R.; Al-Amiery, A.; Al- Majedy, Y.; Design, Synthesis and Bioassay of Novel Coumarins, *Afr. J. Pure Appl. Chem*., **2010**, *4*, 74-86.
21. Samir, A.; Rumez, R.; Fadhil, H.; Synthesis and characterization of some New Oxazepine Compounds Containing 1,3,4-Thiadiazole Ring Derived from D- Erythroascorbic Acid, *Int. J. Appl. Chem*., **2017**, *13*, 393-407.
22. McDonnell, G.; Russell, A.; Antiseptics and Disinfectants: Activity, Action, and Resistance, *Clinic.l Microbio. Rev*., **1999**, *12*, 147-179.
23. Owaid, M.; Muslim, R.; Hamad, H.; Mycosynthesis of Silver Nanoparticles using Terminia sp. Desert Truffle, Pezizaceae, and their Antibacterial Activity, *JJBS*. 1018, **11**, 401-405.